Exploration of Dimethylzinc-Mediated Radical Reactions.

AUTHOR(S):

Yamada, Ken-Ichi; Tomioka, Kiyoshi

Personal Account

THE CHEMICAL RECORD

Exploration of Dimethylzinc-Mediated Radical Reactions

Ken-ichi Yamada,[a] and Kiyoshi Tomioka[b]
[a] Graduate School of Pharmaceutical Sciences, Kyoto University
E-mail: yamak@pharm.kyoto-u.ac.jp
[b] Department of Medicinal Chemistry, Faculty of Pharmaceutical Sciences, Doshisha Women's College of Liberal Arts
E-mail: ktomioka@dwc.doshisha.ac.jp

Received: [will be filled in by the editorial staff]
Published online: [will be filled in by the editorial staff]

ABSTRACT: In this account, our studies on radical reactions that are promoted by dimethylzinc and air are described. Advantages of this reagent and differences from conventional radical initiators, such as triethylborane, are discussed.

Keywords: radical reaction, dimethylzinc, C(sp^3)–H bond functionalization, C–C bond formation, Umpolung

Introduction

It has been long time since the word "radical" changed its meaning in chemistry. In the beginning, a substituent that was unchanged during reactions was referred to as a "radical". Thus, a "methyl radical" was used in almost the same meaning as a "methyl group". In 1900, Gomberg showed for the first time the existence of a molecular entity having an unpaired electron,[1] which was then called "free radical", meaning a "radical" not bound to a molecule. Nowadays, the use of just "radical" to mean what was once called "free radical" is recommended in the chemical community.[2] Although the utility of radical species in organic synthesis is unquestionable, and developments in modern organic synthesis owe much to the field of radical chemistry,[3] it did not draw much attention of synthetic chemists for the first 60 years from its discovery. As found in the recollections by Ingold and Chatgilialoglu, "so far as the vast majority of chemists were concerned, radicals were overly reactive species of no practical value or interest since all radical-mediated reactions were presumed to give gunk and tars,"[4] and "most chemists have avoided radical reactions as messy, unpredictable, unpromising, and essentially mysterious."[5] Synthetic application of radical chemistry was pioneered in 1960 by Barton, who developed useful functional group transformations via a radical process.[6] The mid-1980s marked the start of regular reports on radical chemistry-based synthetic methods when Curran[7] and Stork[8] reported brilliant natural product syntheses, showing the power of radical cyclization reactions as a synthetic tool.[9] This may partly owe to the availability of radical kinetic data starting from the 1980s[10] and a useful radical mediator, tributyltin hydride.[11]

In radical chain reactions, a mediator, such as tributyltin hydride, plays an important role. When radical species A• undergoes addition to B=C bond, radical A–B–C• is produced (eq 1). The keys to successfully obtain A–B–C–H are (1) fast hydrogenation of A–B–C• to prevent undesired reactions, such as polymerization via the further addition to another molecule of B=C (eq 2), and (2) efficient regeneration of A• to propagate the chain reaction. Unless the reaction of A–B–C• with A–H (eq 3) is sufficiently fast to give A–B–C–H and A•, an appropriate mediator M–H is required to hydrogenate A–B–C• (eq 4). The resulting M• would then regenerate A• by the reaction with A–X (eq 5). The mediator and reaction conditions should be chosen carefully to avoid undesired reactions, such as A• + M–H and M• + B=C.

$$A\bullet + B{=}C \longrightarrow A{-}B{-}C\bullet \quad (1)$$

$$A{-}B{-}C\bullet + B{=}C \longrightarrow A{-}B{-}C{-}B{-}C\bullet \longrightarrow \text{polymerization} \quad (2)$$

$$A{-}B{-}C\bullet + A{-}H \longrightarrow A{-}B{-}C{-}H + A\bullet \quad (3)$$

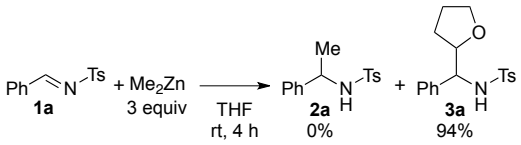
$$A{-}B{-}C\bullet + M{-}H \longrightarrow A{-}B{-}C{-}H + M\bullet \quad (4)$$

$$M\bullet + A{-}X \longrightarrow A\bullet + M{-}X \quad (5)$$

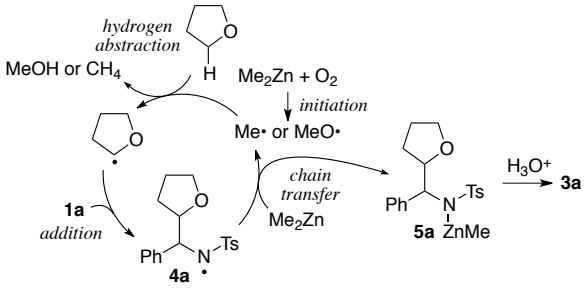
The choice of initiator is also important because it determines the conditions required for the initiation. For radical chain reactions, substoichiometric initiators, such as azo compounds,[12] distannanes,[13,14] and peroxides,[12] are often used with heat or irradiation. The use of trialkylboranes, mainly triethylborane, with air as a radical initiator allows us to perform radical reactions even at –78 °C.[15] Stoichiometric metal salts were also used to generate radical species from closed shell organic compounds by a single electron transfer process. Low-valent metal species, such as samarium(II) and titanium(III), generate ketyl radicals from carbonyl compounds.[9a,16,17] Oxidants, such as manganese(III) and cerium(IV), are used to form electrophilic radicals from electron-rich olefins and enolates.[9h,18] In short, the appropriate radical initiator and mediator depend on the reaction conditions and substrates utilized. Therefore, their development has greatly contributed to advancements in radical chemistry.[3] We accidentally found that dimethylzinc acts as both an initiator and a mediator.

Discovery of a radical reaction with dimethylzinc–air

Due to the chemical and medicinal importance of optically active amines,[19,20] we have been engaged in developing methodologies for asymmetric synthesis of chiral amines.[21,22,23,24,25,26,27] During the course of the study, we examined an addition reaction of dimethylzinc to *N*-tosyl (Ts) imine **1a** in tetrahydrofuran (THF), and encountered an addition reaction of the solvent THF3 to the imine to give THF adduct **3a**, instead of the expected methyl adduct **2a** (Scheme 1).[28] The reaction failed to proceed in the absence of either dimethylzinc or air. Accordingly, radical species were expected to be involved in the reaction. A plausible mechanism is shown in Scheme 2. The chain reaction is initiated by the reaction of dimethylzinc and air to form methyl and methoxyl radicals, which abstract a hydrogen atom at the α-position of THF. The resulting THF-2-yl radical undergoes addition to the C=N bond of **1a** to give aminyl radical **4a**. The subsequent homolytic substitution (S_H2 reaction) at dimethylzinc produces methyl radical, which starts another chain of the reactions, and zinc amide **5a**, which gives **3a** after aqueous work-up. The following features of this reaction immediately attracted us: (1) A non-acidic C(sp^3)–H bond, the α-C–H bond of THF, is functionalized in high efficiency under mild conditions, (2) Latent polarity of THF is reversed, that is, Umpolung of α-oxygenated alkane occurs, and (3) Dimethylzinc, an uncommon reagent in radical reactions, initiates and mediates the reaction. In this account, we discuss the results of our studies having started from this finding.[29]



Scheme 1. Unexpected addition of THF to imine **1a**.



Scheme 2. Plausible mechanism of the reaction.

Ken-ichi Yamada was born in 1973 in Tokyo, Japan. He completed his Ph.D. under the supervision of Professor Masakatsu Shibasaki in 2001 (University of Tokyo, Japan). He joined Kyoto University as an Assistant Professor in 2001 and has been an Associate Professor since 2006. He received the Pharmaceutical Society of Japan Award for Young Scientists in 2007. His research interests are in synthetic organic chemistry, asymmetric synthesis, and organometallic chemistry.

Kiyoshi Tomioka, born in 1948 in Tokyo, Japan, is a Professor of Doshisha Women's College of Liberal Arts. He received his Ph.D. from the University of Tokyo in 1976 under the direction of Prof. S. Yamada. He worked as a postdoctoral fellow with Prof. A. I. Meyers at Colorado State University in 1976–1978. He joined the University of Tokyo as a Research Associate in 1978 and was promoted to Associate Professor in 1983. He moved to Osaka University as a Professor in 1992, and then to Kyoto University in 1996. He has been a Professor at Doshisha Women's College of Liberal Arts since 2010. He received The Pharmaceutical Society of Japan Award in 2003. His research interests are in synthetic organic chemistry, asymmetric synthesis, organometallic chemistry, and molecular architecture.

Initiation step

Radical initiation by triethylborane

Triethylborane[15] and diethylzinc[30] were frequently used as radical initiators in organic synthesis, although dimethylzinc was an uncommon initiator. The utility of organoboron as radical initiators was first reported in olefin polymerization in 1957.[31] Nowadays, autoxidation of organoborons, especially triethylborane, is a widely utilized method to initiate radical reactions.[15] Much effort has been made to clarify the mechanism of the autoxidation.[32,33] Although it has not been fully understood, the plausible mechanism at present is as follows: Alkylperoxyborane is initially produced presumably via simultaneous or stepwise alkyl migration of oxygen-coordinated boron (eq 6), although an alternative caged S_H2–recombination mechanism (eq 7) is not completely excluded.[34] Homolytic cleavage of the O–O bond then occurs to give O-centered radicals (eq 8). Interestingly, this step does not proceed without triakylborane.[33b,33f] These O-centered radicals further react with trialkylborane to generate alkyl radicals (eqs 9 and 10).

$$R_3B + O_2 \longrightarrow \underset{\substack{R \quad O^+}}{R_2\bar{B}-O} \longrightarrow R_2BOOR \qquad (6)$$

$$\text{or } R_3B + O_2 \longrightarrow (R_2BOO^{\bullet} + R^{\bullet}) \longrightarrow R_2BOOR \qquad (7)$$

$$R_2BOOR + R_3B \longrightarrow R_2BO^{\bullet} + RO^{\bullet} + R_3B \qquad (8)$$

$$R_2BO^{\bullet} + R_3B \longrightarrow R_2BOBR_2 + R^{\bullet} \qquad (9)$$

$$RO^{\bullet} + R_3B \longrightarrow R_2BOR + R^{\bullet} \qquad (10)$$

The generation of alkyl and alkoxyl radicals were both confirmed by spin-trapping with ESR[35] and MS.[36] It is noteworthy that more alkoxyl and less alkyl radicals were observed as the concentration of trialkylborane was lowered.[35] This observation strongly supports the above mechanism; it is the reaction of the O-centered radicals and trialkylborane that generates alkyl radicals (eqs 9 and 10). Therefore, the autoxidation is likely not as simple as the direct generation of alkyl radicals by the S_H2 reaction of trialkylborane and triplet oxygen (eq 11).[15,32b]

$$R_3B + O_2 \longrightarrow R_2BOO^{\bullet} + R^{\bullet} \qquad (11)$$

Radical initiation by dialkylzinc

Initiation of a radical reaction by dialkylzinc was also found in olefin polymerization in 1959.[37] In contrast to trialkylborane, not so many reports were available about the autoxidation of dialkylzinc.[33c,h,j,38] As with trialkylborane, the initial product of the autoxidation was identified as alkylperoxyzinc species (eq 12).[39] Recently, the formation of both alkyl and alkoxyl radicals in the autoxidation of dialkylzinc was confirmed by spin-trapping with ESR.[40] Therefore, it would be reasonable to assume that the mechanism is as shown in eqs 13–15, although it is unclear whether or not it requires dialkylzinc for the second step to proceed as in the case of trialkylborane.[33b,33f]

$$R_2Zn + O_2 \longrightarrow RZnOOR \qquad (12)$$

$$RZnOOR \longrightarrow RZnO^{\bullet} + RO^{\bullet} \qquad (13)$$

$$RZnO^{\bullet} + R_2Zn \longrightarrow RZnOZnR + R^{\bullet} \qquad (14)$$

$$RO^{\bullet} + R_2Zn \longrightarrow RZnOR + R^{\bullet} \qquad (15)$$

Later, we found that the radical reaction was initiated with dimethylzinc and *tert*-butyl hydroperoxide in the absence of air.[41,42] This also supports the above mechanism. Probably, an alkylperoxyzinc species is formed with the evolution of methane (eq 16) and the subsequent homolysis (eq 13) takes place.

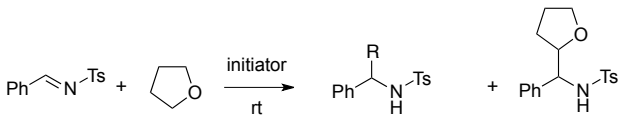
$$Me_2Zn + t\text{-}BuOOH \longrightarrow MeZnOOt\text{-}Bu + CH_4 \qquad (16)$$

Both trialkylborane and dialkylzinc species are pyrophoric and ignite on contact with air, so that they are used for a rocket igniter. It should be noted that the neat compounds must be handled with special care. However, dimethylzinc and some other species (Me_2Zn, Et_2Zn, $i\text{-}Pr_2Zn$, Bu_2Zn, Et_3B, and Bu_3B) are commercially available as a hydrocarbon solution, which has much less reactivity towards air. This allows us to use these reagents with usual care that is taken in the use of common organometallic solutions, such as normal butyllithium, and makes these reagents suitable for organic synthesis.

The influence of the radical initiator

We first examined the reaction of **1a** and THF using other radical initiators (Table 1). Other dialkylzinc reagents such as diethyl, diisopropyl, and diphenylzinc were less efficient, producing significant amounts of alkyl adducts **2b–d** as well as the reduced product **2e**.

Table 1. Effect of the radical initiator on the addition of THF to **1a**.



1a

2a: R = Me **2d**: R = Ph
2b: R = Et **2e**: R = H
2c: R = *i*-Pr

3a

initiator	equiv	time (h)	yield of **2**	yield of **3a**
Me_2Zn	3	4	not detected	94%
Et_2Zn	3	4	**2b** 33%, **2e** 2%	48%
$i\text{-}Pr_2Zn$	3	4	**2c** 34%, **2e** 27%	6%
Ph_2Zn	3	4	**2d** 7%	not detected
Et_3B	3	48	**2b** 29%	not detected
Bz_2O_2[a]	0.1	24	not detected	trace

[a] Conducted in refluxing THF.

The formation of alkyl adducts **2b–d** could be understood in terms of the nucleophilicity of the alkyl radicals generated from the dialkylzinc reagents, except for diphenylzinc. The nucleophilicity (*i*-Pr$^{\bullet}$ > Et$^{\bullet}$ > Me$^{\bullet}$) is in inverse proportion to the yield of **3a**. The more nucleophilic the alkyl radical is, the more the addition of the alkyl radical should compete. In addition, diisopropylzinc acted as a hydride donor to give **2e**. The bond dissociation energy (BDE) of the R–H bond would also be important. The BDE (Me–H, 439; Et–H, 421; *i*-Pr–H, 411 kJ/mol)[43] is proportional to the yield of **3a**. As the BDE decreases, the hydrogen abstracting ability of the corresponding alkyl radical presumably reduces, and therefore, less THF-2-yl radicals should form in the reaction. The advantage of dimethylzinc, therefore, would be the generation of the least nucleophilic and most unstable alkyl radical, methyl radical, as well as the absence of a β-hydride. Moreover, the concentration of O-centered radical species is higher in the reaction mixture of dimethylzinc–air than that in the case of diethylzinc–air.[40] This is probably because the reaction of O-centered radicals and dimethyl zinc (eqs 14 and 15) is unfavorable compared to triethylborane and other dialkylzincs due to instability of the forming methyl radical. The high concentration of O-centered radicals could also increase the rate of the hydrogen abstraction, because hydrogen abstraction by alkoxyl radicals is much faster than that by alkyl radicals.[44] Phenyl radicals might be too unstable to form effectively from diphenylzinc.

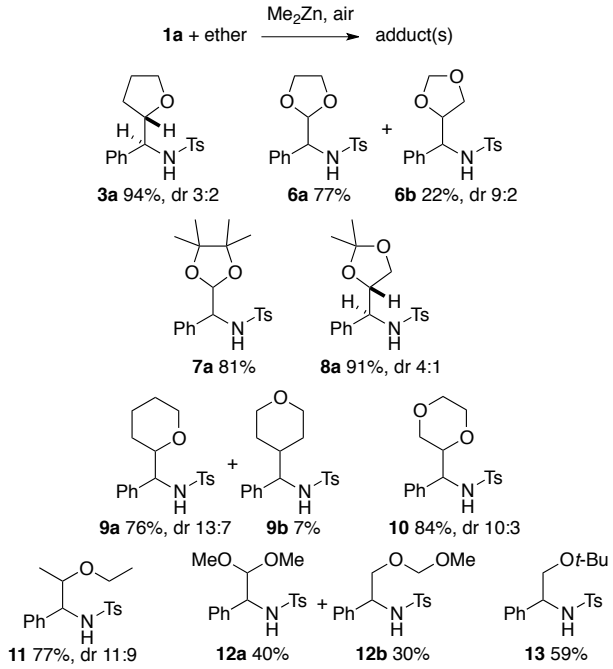
Conventional radical initiators such as triethylborane[42,45] and dibenzoyl peroxide[46] were totally inefficient. When triethylborane was used, ethyl adduct **2b** was produced with no detectable amount of **3a** in the crude product. The difference from the reaction using diethylzinc is interesting yet not fully understood. Possibly, the concentration of ethoxyl radicals is higher in the reaction mixture with diethylzinc than with triethylborane, which might quench ethoxyl radicals more quickly (eq 10). In the reaction using dibenzoyl peroxide, **1a** was almost quantitatively recovered after 24 h. This result clearly indicates that the direct abstraction of a hydrogen atom from THF by aminyl radical **4a** should be a minor pathway and dialkylzinc or triethylborane, which traps the aminyl radical intermediates, is required for the addition reactions to proceed smoothly. This also explains the requirement of an excess amount of dimethylzinc for complete conversion of **1a**.

Hydrogen abstraction step: generation of other carbon-centered radicals

Alkoxyalkyl radicals from ethers

As shown in Scheme 3, cyclic ethers were generally good nucleophiles to give aminobenzylated ethers in good yields. The hydrogen atoms at the α-position of the ethers were preferentially replaced by an aminobenzyl group. Although the ethers were usually used as a solvent in the reactions (125–270 equiv), the amount was reducible with iron salt as an additive.[47]

When there are more than two non-equivalent hydrogen atoms next to the oxygen functionality, regioselectivity was usually not sufficient; the reaction of 1,3-dioxolane quantitatively produced a 7:2 regioisomeric mixture of **6a** and **6b**. This regioselectivity is in good agreement with the reported relative rate of hydrogen abstraction at the 2- and 4-positions by *tert*-butoxyl radical (3:1 at 60 °C).[48] This indicates that O-centered radical species rather than methyl radical should mainly abstract the hydrogen atom.[49]



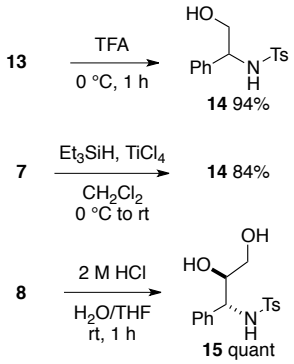
Scheme 3. Addition of ether to **1a**.

THF and 1,3-dioxolane gave products **3a** and **6a**,**b** in better yields (94–99%) than their 6-membered analogues, tetrahydropyran (THP) and 1,4-dioxane (**9a**,**b** and **10**, 83–84%). This is probably due to faster hydrogen abstraction from 5-membered cyclic ethers[50,51] because of the back-hyperconjugation[52] and release of the ring strain in the formed radical. Probably, the back-hyperconjugation also contributes to increasing the nucleophilicity of the radicals. Interestingly, regioisomer **9b** was obtained in the reaction of THP. This also likely reflects the decreased radical stabilizing ability of the oxygen atom in the 6-membered ring.[50]

Acyclic ethers, such as diethyl ether, dimethoxymethane, and *tert*-butyl methyl ether, gave products **11**–**13** in good but lower yields (59–77%) than cyclic ethers (81–99%).

Better results were obtained when larger excess amounts (270–500 equiv) of acyclic ethers were utilized. Dimethoxymethane gave a 4:3 mixture of regioisomers **12a**,**b**. In general, the diastereoselectivity was fair (11:9–4:1).

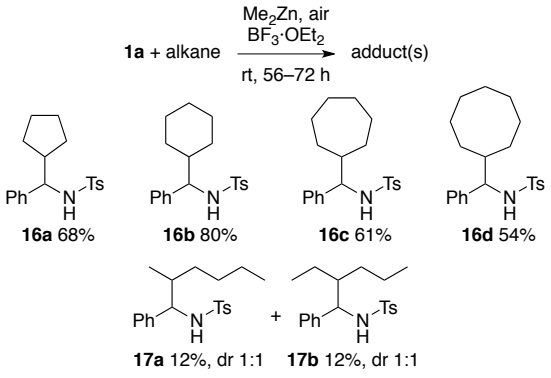
tert-Butyl ether **13**, the product of the reaction with *tert*-butyl methyl ether, was converted into amino alcohol **14** in high yield (Scheme 4).[53] Thus, *tert*-butyl methyl ether is a hydroxymethyl anion equivalent. 4,4,5,5-Tetramethyl- and 2,2-dimethyldioxolanes were also utilized as oxygenated C1 and C2 units; adducts **7** and **8** were converted into amino alcohols **14** and **15** in good yields.[53,54]



Scheme 4. Conversion of ether-adducts into amino alcohols.

Generation of alkyl radicals from alkanes

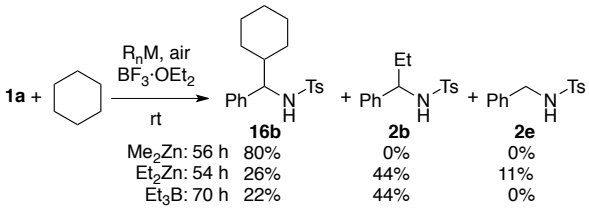
Thanks to low nucleophilicity and stability of methyl radicals, the dimethylzinc–air condition was also suitable for direct generation of alkyl radicals from alkanes.[55] The reaction gave better results with large excess amounts (500 equiv) of cycloalkanes, and adducts **16a–d** were produced from 5- to 8-membered cycloalkanes in good yields (Scheme 5).



Scheme 5. Addition of alkane to **1a**.

In this reaction, the addition of trifluoroborane diethyl etherate improved the yield of the products. Probably, the Lewis acid lowered the energy level of the LUMO of **1a** by complexation and increased the rate of the radical addition step. Although the yield was low and regioselectivity was uncontrolled, an acyclic alkane, hexane, also produced adducts **17a**,**b**.[56] The adduct of 1-hexyl was not detected in this reaction, probably due to the following reasons: (1) abstraction of the terminal methyl hydrogen of hexane is most unfavorable, and (2) a primary alkyl radical, 1-hexyl, is less nucleophilic than the secondary alkyl radical species.

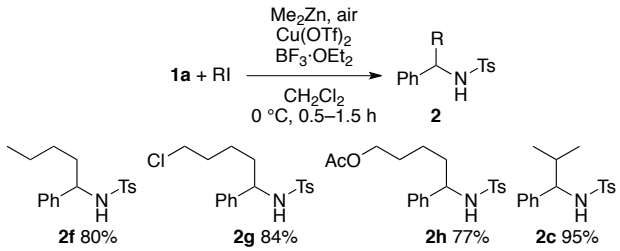
Dimethylzinc showed higher performance than diethylzinc and triethylborane in this reaction as well (Scheme 6). With diethylzinc or triethylborane, less cyclohexyl adduct **16b** and more ethyl adduct **2b** were produced. This is also explainable by the lower nucleophilicity of methyl radical than that of ethyl radical, as well as higher concentration of methoxyl radical than that of ethoxyl radical as previously discussed.



Scheme 6. Higher performance of dimethylzinc in the reaction of **1a** and cyclohexane compared to diethylzinc and triethylborane.

Generation of primary alkyl radicals from 1-iodoalkanes

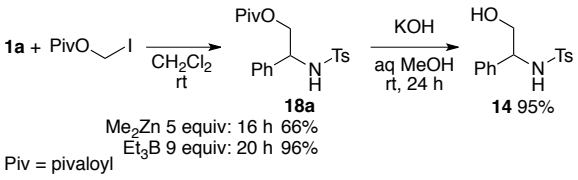
Because of the lower stability of a primary alkyl radical than secondary and tertiary alkyl radicals, its generation by halogen abstraction usually requires stoichiometric tin compounds and haloalkanes.[57] Even though dimethylzinc–air generates methyl radicals, which are less stable than primary alkyl radicals, the direct generation of a primary alkyl radical from alkane was unsuccessful due to predominant hydrogen abstraction from methylene groups as mentioned above. However, dimethylzinc–air enables the generation of primary alkyl radicals from 1-iodoalkanes via iodine abstraction without the use of tin compounds (Scheme 7).[56]



Scheme 7. Addition of alkyl iodide to **1a**.

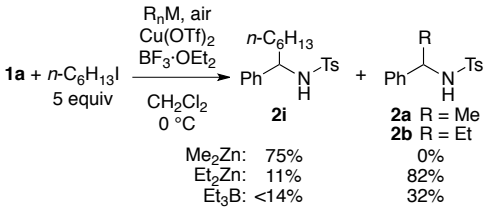
The reaction likely involves the addition of a primary alkyl radical rather than alkylzinc species because (1) only a trace amount of the product was obtained in the absence of air, (2) the production of the methyl adduct **2a** was only negligible either in the presence or absence of air, and (3) the formation of alkylzinc species from alkyl iodides and dimethylzinc is unlikely because the process would involve the formation of the less stable methyl radical from a more stable primary or secondary alkyl radical via S_H2 process.[58] Labile functionalities under anionic conditions, such as the chlorine atom of **2g** and the ester group of **2h**, were tolerated. While the addition of primary alkyl radicals required 5 equiv of the corresponding iodide (**2f**–**h**), 1.5 equiv was sufficient for the addition of the secondary alkyl radical (**2c**). This is probably due to the lower stability and nucleophilicity of the primary alkyl radicals than the secondary alkyl radical.

In this reaction, the yields of the products were significantly decreased in the absence of either copper triflate or trifluoroborane diethyl etherate. The copper salt may function as a Lewis acid and/or facilitate the generation of methyl radical.[59] In this reaction, activation of the C=N bond by Lewis acids was required probably because of the low nucleophilicity of primary alkyl radical species. Indeed, the addition of a more nucleophilic radical, acyloxymethyl radical, which has an oxygen functionality at the α-position, proceeded smoothly in the absence of Lewis acids (Scheme 8).[60] The product **18a** was easily hydrolyzed to give amino alcohol **14**. In this reaction, the use of triethylborane in place of dimethylzinc was beneficial to give the product more cleanly in higher yield, albeit longer reaction time was required.



Scheme 8. Addition of iodomethyl ester to **1a**.

In these reactions, it is probably methyl radical that abstracts iodine from iodoalkanes because iodine abstraction by O-centered radical species is quite unlikely on the basis of the BDE of O–I and Me–I bonds (213 and 239 kJ/mol, respectively).[43] Therefore, not only methoxyl radical but also methyl radical should exist at effective concentration in the reactions of dimethylzinc–air. Although C-centered radicals should form at higher concentration with diethylzinc and triethylborane, the use of these radical initiators in this reaction resulted in the production of a significant amount of ethyl adduct **2b** (Scheme 9).



Scheme 9. Higher performance of dimethylzinc in the reaction of **1a** and 1-iodohexane compared to diethylzinc and triethylborane.

This result is noteworthy because the iodine exchange between primary alkyl radical species is a fast reaction,[61] and an excess amount of 1-iodohexane was utilized in the reaction. Therefore, the formation of **2b** as a major product suggests that the addition of ethyl radical to **1a** might be fast enough to compete with the iodine abstraction. The low nucleophilicity and stability of methyl radical is advantageous in this reaction to allow exothermic iodine abstraction to generate primary alkyl radical before the addition of methyl radical takes place.

Addition step: other radical acceptors

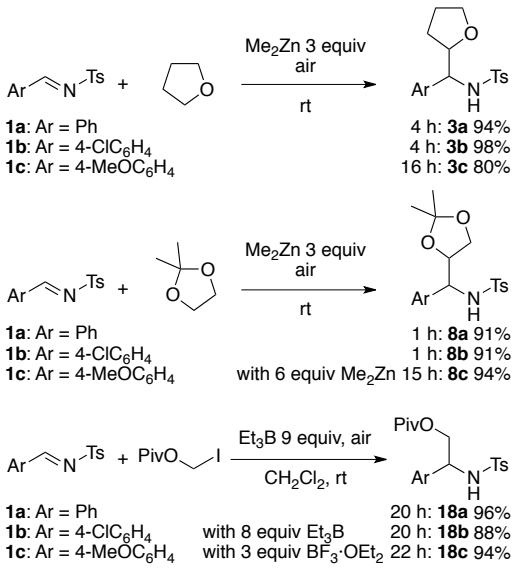
Electronic influence of *C*-substituents of the imine

Imines bearing other *C*-substituents, such as a substituted phenyl group (*o*- and *p*-tol, *p*-anisyl, *p*-chlorophenyl, and 1- and 2-naphthyl), a heteroaromatic ring (2- and 3-pyridyl, and 2-furyl), and an alkyl group (2-phenylethyl and cyclohexyl), were applicable to the addition reactions.[28,53,54,55,56,60] The reaction efficiency was affected by the electronic character of the imine. The reactions of the electron-deficient *p*-chlorobenzaldimine generally proceeded smoothly, while those of the electron rich *p*-anisaldimine were retarded and required more reagents and/or longer reaction time for completion (Scheme 10). Particularly, the addition of trifluoroborane diethyl etherate as a Lewis acid was required for the reaction of *p*-anisaldimine **1c** with iodomethyl pivalate to complete. These results clearly indicate that these radical additions are governed by the interaction between the SOMO of the nucleophilic radicals and the LUMO of the imines.

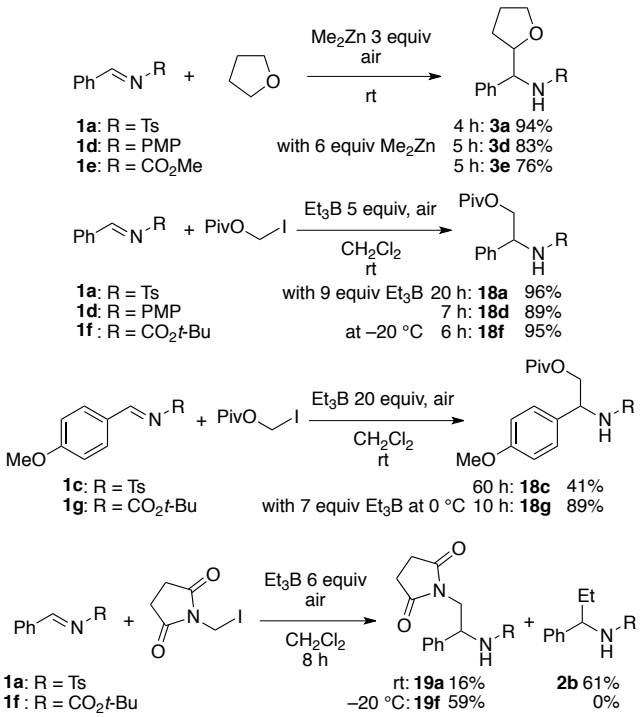
Imines having other *N*-substituents

Imines bearing other types of *N*-substituents were also applicable, and the best choice of the substituent likely depends on the reaction conditions. In the reaction of THF with dimethylzinc–air, *N*-*p*-methoxyphenyl (PMP) imine **1d** gave the product **3d** more slowly and required twice the amount of dimethylzinc than *N*-Ts imine **1a** (Scheme 11).[62] In contrast, **1d** reacted more rapidly to give **18d** than

1a to give **18a** in the reaction of iodomethyl pivalate with triethylborane–air.



Scheme 10. Electronic effect on the radical addition to imine.



Scheme 11. Effect of *N*-substituents on the addition reactions to imine.

These results suggest that the rate-determining step of the reaction with dimethylzinc would be the addition step (Scheme 2), whilst the rate-determining step with triethylborane is the trap of the aminyl radical. Accordingly, the reaction of **1a**, having a LUMO of lower energy level, should be faster when dimethylzinc is used, and on the contrary, the reaction of **1d**, which produces a more Lewis basic aminyl radical, should be faster with triethylborane.

Alternatively, there is a possibility that activation of the imines by triethylborane as a Lewis acid is operative in the radical addition reactions.[63,64,65] Triethylborane can only make a complex with the more Lewis basic imine, **1d**, which then undergo the addition reaction more smoothly than non-activated **1a**.

Recently, we found that *N*-alkoxycarbonyl imines are highly superior acceptors in triethylborane-mediated radical addition reactions.[66] The reaction of *N*-*tert*-butoxycarbonyl (Boc) imine **1f** with iodomethyl pivalate at –20 °C was even faster than that of *N*-PMP imine **1d** at room temperature (Scheme 11). Comparing the reactions of electron-rich *p*-anisaldimines **1c** and **1g** highlights the high performance of *N*-alkoxycarbonyl imines. Without trifluoroborane diethyl etherate, the reaction of *N*-Ts imine **1c** did not reach to completion even after 60 h at room temperature using excess amount of triethylborane. In contrast, the reaction of *N*-Boc imine **1g** completed after 10 h at 0 °C to give product **18g** in high yield.

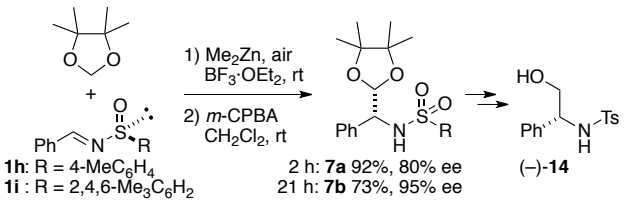
The high performance of the *N*-Boc imines is also explainable in terms of the LUMO energy level of the imines and the Lewis basicity of the resulting aminyl radicals. Because the pK_a value of a carbamate (EtO_2CNH_2, 24.2)[67] is between those of a sulfonamide ($PhSO_2NH_2$, 16.1)[68] and an aniline ($PhNH_2$, 30.6),[69] the electron-withdrawing character of a Boc group should lie between a Ts and a PMP group. Therefore, *N*-Boc imines should have LUMOs with lower energy level and be more reactive toward nucleophilic radicals than *N*-PMP imines. At the same time, the resulting *N*-Boc aminyl radicals should have higher Lewis basicity and react more rapidly with triethylborane to propagate the chain reactions than *N*-Ts aminyl radicals. The superiority of an *N*-alkoxycarbonyl imine over an *N*-Ts imine was not observed in the reaction with dimethylzinc; the reaction of *N*-methoxycarbonyl imine **1e** was slightly slower than that of **1a**. This is consistent with the above-mentioned assumption that the addition step should be the rate-determining step in the reaction with dimethylzinc.

The results with *p*-anisaldimines **1c** and **1g**, however, cannot be fully explained by the above-mentioned two factors. As described above (Scheme 10), trifluoroborane diethyl etherate accelerates the reaction of **1c**. This indicates that not the aminyl radical trap but the addition step should become rate-determining when an electron-rich imine is utilized as a radical acceptor, even in the reaction using triethylborane. Therefore, the reaction in Scheme 11 indicates that *N*-Boc imine **1g** is more reactive toward pivaloyloxymethyl radical than *N*-Ts imine **1c**; the order of the reactivity is contradictory to the aforementioned

electron-withdrawing power of the substituents. It is a plausible explanation that triethylborane activates *N*-alkoxycarbonyl imines bearing an electron-donating aromatic ring by complexation, but does not activate *N*-Ts imines. However, we have not yet succeeded in observing a sign of the complexation either in ^{1}H, ^{13}C, or ^{11}B NMR of the mixture of **1f** and triethylborane.[70,71,72]

N-Alkoxycarbonyl imine showed its quality as a good radical acceptor also in the addition reaction of imidomethyl radical.[73] The imidomethyl radical, which was generated from *N*-iodomethylsuccinimide using triethylborane, reacted with *N*-Boc imine **1f** to give 1,2-diamine **19f**. In contrast, *N*-Ts imine **1a** mainly gave ethyl adduct **2b**, and the imidomethylated product **19a** was marginally produced.

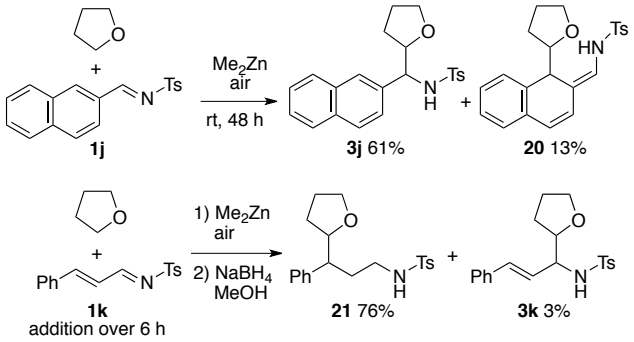
An asymmetric reaction was realized using enantioenriched *N*-sulfinyl imines (Scheme 12).[54] Tetramethyldioxolane underwent addition to **1h** with 9:1 diastereoselectivity, and gave **7a** with 80% ee after oxidation by *m*-chloroperbenzoic acid (*m*-CPBA). Because of the lower electron-withdrawing power of the sulfinyl group than that of a Ts group, the addition of trifluoroborane diethyl etherate was necessary for the reaction to proceed smoothly. To the best of our knowledge, this is the first example of a radical addition reaction to *N*-sulfinyl imines.[74] The diastereoselectivity was enhanced when **1i**, bearing a more bulky sulfinyl group, was employed.[75] Both adducts were converted into optically active amino alcohol (–)-**14**.



Scheme 12. Asymmetric radical addition to *N*-sulfinyl imines.

α,β-Unsaturated imines

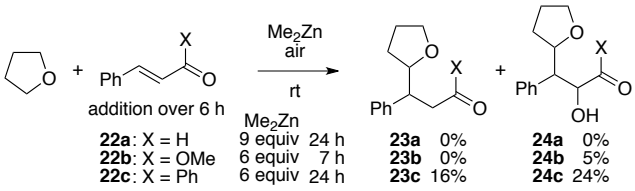
Although the reaction of naphthaldimine **1j** and THF gave product **3j** as a major product, a significant amount of the conjugate addition product **20** was also obtained (Scheme 13).[29a] This result indicates that conjugate addition should occur when α,β-unsaturated imines are employed. Indeed, the reaction of cinnamaldimine **1k** with THF preferentially provided the conjugate addition product **21** after reduction of the imine moiety.[76] Dropwise addition of **1k** over 6 h was important to obtain **21** in good yield (*vide infra*).



Scheme 13. Conjugate addition of THF to α,β-unsaturated imines.

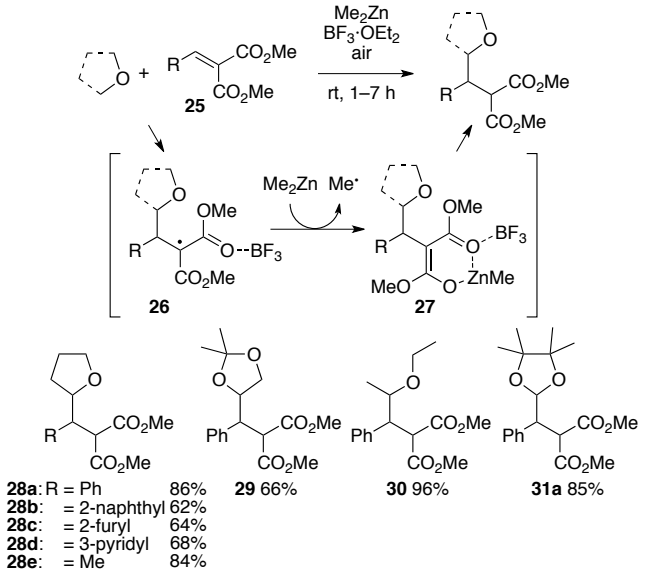
α,β-Unsaturated carbonyl compounds

Encouraged by the above results, the reactions of cinnamaldehyde (**22a**), methyl cinnamate (**22b**), and chalcone (**22c**) with THF were attempted (Scheme 14).[77] Although the reaction of **22c** produced the desired adduct **23c** in 16% yield along with 24% of an α-hydroxylated adduct **24c**, only a complex mixture and a small amount of the hydroxylated adduct **24b** resulted from the reactions of **22a** and **22b**, respectively. These results clearly show that the enoxyl radicals resulting from the addition of THF-2-yl radical should have inferior stability and reactivity toward dimethylzinc to those of the *N*-Ts enamidyl radicals resulting from **1k**.



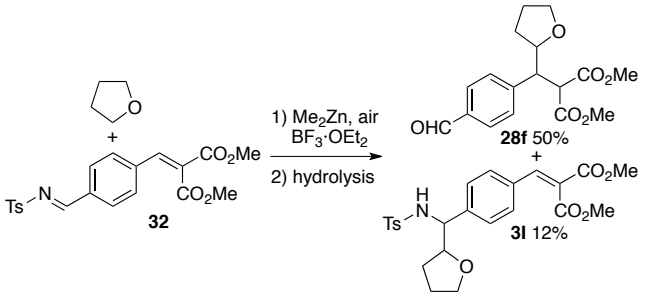
Scheme 14. Attempted addition of THF to α,β-unsaturated carbonyl compounds.

Further investigation led us to find alkylidenemalonate **25** as a good radical Michael acceptor of a synthetic equivalent of cinnamate. Conjugate addition of ethers to **25** proceeded using dimethylzinc and was facilitated in the presence of trifluoroborane diethyl etherate (Scheme 15).[78] The reaction likely proceeds via intermediate radical **26**, which is stabilized by the two electron-withdrawing groups. Dimethylzinc then traps **26** and regenerates methyl radical to form zinc enolate **27**, which is converted into products **28**–**31** after hydrolysis.[79]



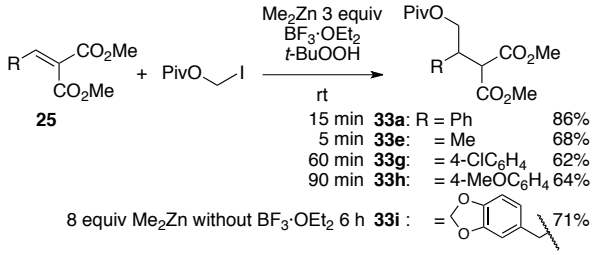
Scheme 15. Conjugate addition of ethers to alkylidenemalonates.

The competitive reaction using **32** revealed that the C=C bond of alkylidenemalonate is a superior radical acceptor to the C=N bond of *N*-Ts imine, producing aldehyde **28f** rather than amine **3l** as a major product after hydrolysis (Scheme 16).



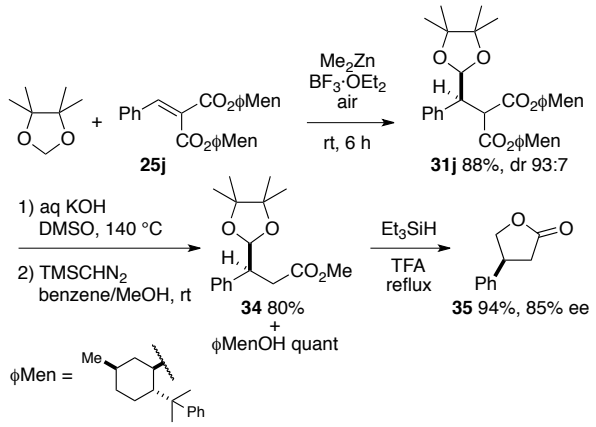
Scheme 16. Competitive reaction between alkylidenemalonate and *N*-Ts imine moieties.

Alkylidenemalonate **25** was also applicable to conjugate addition of acyloxymethyl (Scheme 17).[41] Notably, phenethylidenemalonate, prone to olefin migration, was applicable, and **33i** was obtained in good yield. This malonate **25i**, however, was incompatible with the Lewis acid, and this resulted in the requirement of longer reaction time and more dimethylzinc. It was important to conduct this reaction under argon atmosphere to prevent autoxidation of pivaloyloxymethyl radical (*vide infra*). The reaction was probably initiated by zinc *tert*-butyl peroxide formed *in situ* (eqs 16 and 13).



Scheme 17. Conjugate addition of pivaloyloxymethyl to alkylidenemalonates.

To realize an asymmetric variant of this reaction, an 8-phenylmenthyl group (ϕMen) was an appropriate chiral auxiliary. The conjugate addition of teteramethyldioxolane to **25j** provided **31j** with 93:7 facial selectivity (Scheme 18).[78] The dioxolane is a hydroxymethyl anion equivalent; **31j** was converted into chiral lactone **35** without any loss of stereoisomeric purity via mono methyl ester **34**, with quantitative recovery of the chiral auxiliary.

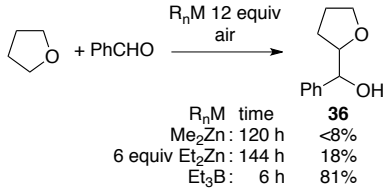


Scheme 18. Diastereoselective conjugate addition to bis-8-phenylmenthyl alkylidenemalonate.

Aldehyde

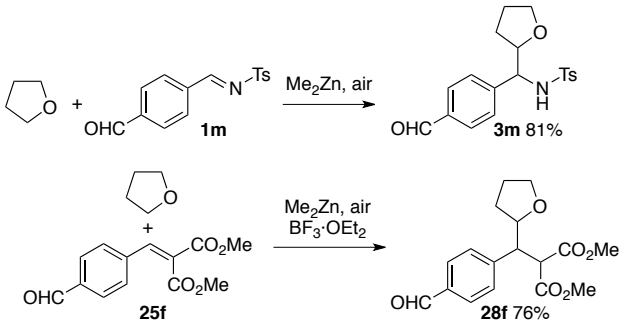
In contrast to the reaction of triethylborane,[42,45] addition of THF to benzaldehyde proceeds only negligibly when dimethylzinc is used (Scheme 19).[62] This is probably due to inadequate reactivity of dimethylzinc toward alkoxyl radicals, which form by the addition of THF-2-yl radical to the C=O bond of the aldehyde. Intramolecular radical addition to an aldehyde is as fast as that to an alkene, although reverse reactions are much faster.[80] Therefore, it is reasonable to assume that the addition of THF-2-yl should occur both in the reactions with dimethylzinc and triethylborane. The reverse reaction[42a] gives back the aldehyde and THF-2-yl radical when dimethylzinc is used, whereas triethylborane could trap the oxyl radical

intermediate to give **36** after hydrolysis. The slow trapping of the intermediate by dimethylzinc could be attributable to the instability of methyl radical, which is released in the S_H2 process as discussed above. Indeed, the reaction using diethylzinc (6 equiv), in which the trapping should be more exothermic due to the stability of ethyl radical, produced a small but notable amount of **36** (18%) after 144 h.[81] As previously proposed, the rapid trapping by triethylborane might be due to the precoordination of the aldehyde to the boron atom when the addition occurs.[42c]



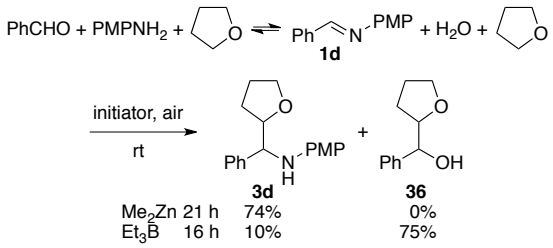
Scheme 19. Marked difference between dialkylzinc and Et_3B in the reaction of THF and benzaldehyde.

Taking advantage of this property, chemoselective reactions of C=N and C=C bonds in the presence of a C=O bond were realized (Scheme 20).[53,62,78] Importantly, C–C bond formation selectively occurred without any protection of the aldehyde moieties of **1m** and **25f** to directly give aldehydes **3m** and **28f**.



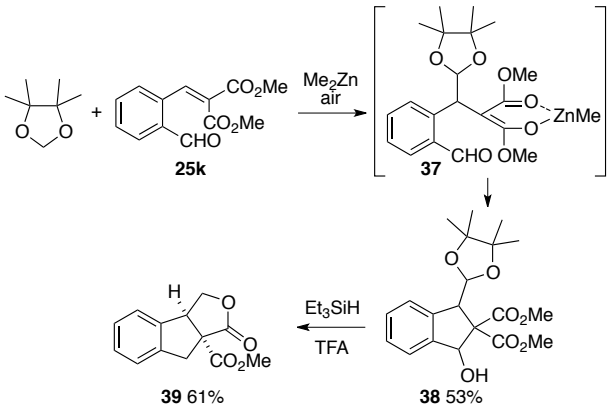
Scheme 20. Chemoselective reactions in the presence of aldehyde.

The three-component reaction of THF, aldehyde, and amine was also realized. Amine **3d** was produced in the reaction of benzaldehyde and *p*-anisidine in THF with dimethylzinc, probably through the addition of THF-2-yl radical to *N*-PMP imine **1d** that is formed *in situ* (Scheme 21).[62] Interestingly, when triethylborane was used in place of dimethylzinc, amine **3d** was a minor product, and alcohol **36** was mainly produced. The high ability of aldehyde as a radical acceptor in the presence of triethylborane was also reported in the literatures.[82]



Scheme 21. Reactions of THF with a mixture of benzaldehyde and *p*-anisidine.

The inertness of the aldehyde functionality enabled a radical addition–aldol-type cyclization cascade (Scheme 22). The dimethylzinc-mediated addition of dioxolane to alkylidenemalonate **25k** gave zinc enolate intermediate **37**, which then underwent an aldol-type cyclization to give **38**.[83] The reduction with triethylsilane in TFA provided tricyclic lactone **39**.



Scheme 22. Radical addition–aldol-type cyclization cascade.

Reactions caused by oxygenated byproducts

The autoxidation of ethers is a well-recognized hazard in laboratories. The reaction of C-centered radical with triplet oxygen is diffusion-controlled,[84] giving peroxyl radical (eq 17), which then results in peroxide and hydroperoxide (eqs 18 and 19). However, we usually observed only a tiny amount of peroxide or hydroperoxide after the reactions with dimethylzinc and air. This is probably because dimethylzinc reduces peroxyl radical and hydroperoxide via zinc peroxide (eqs 20 and 21) to finally give zinc alkoxide (eqs 13–15). This is an important feature of the reactions with dimethylzinc and air from a safety point of view.

$$R^{\bullet} + O_2 \rightarrow ROO^{\bullet} \quad (17)$$

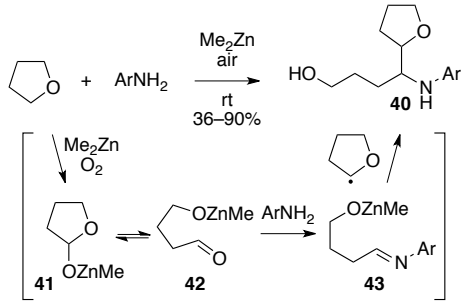
$$ROO^{\bullet} + R^{\bullet} \rightarrow ROOR \quad (18)$$

$$ROO^{\bullet} + RH \rightarrow ROOH + R^{\bullet} \quad (19)$$

$$ROO^{\bullet} + Me_2Zn \rightarrow ROOZnMe + Me^{\bullet} \quad (20)$$

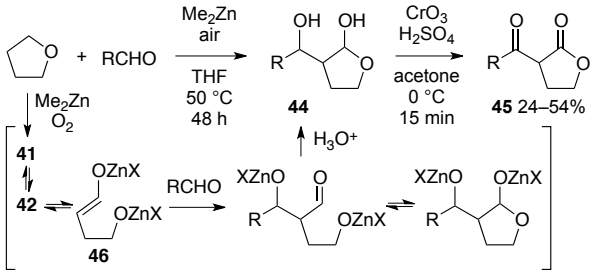
$$ROOH + Me_2Zn \rightarrow ROOZnMe + MeH \quad (21)$$

In the aforementioned radical reactions, a part of the generated C-centered radicals is oxidized by molecular oxygen without undergoing the addition reactions. During the investigation, we observed some products attributable to reactions of these oxygenated byproducts. The first example is amino alcohol **40**, found as a byproduct in the three-component reaction (Scheme 21). This product was obtained in good yield when the reaction was conducted in the absence of an aldehyde (Scheme 23).[85] Probably, oxygenated THF **41**, which is generated via the above-mentioned process, is responsible for the formation of **40**. The ring opening of **41** gives aldehyde **42**, which forms imine **43** with the aniline. The addition of THF-2-yl radical to **43** would provide **40**.



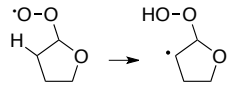
Scheme 23. Formation of amino alcohol **40**.

The second example is lactol **44**, an addition product of α-oxygenated THF to aldehyde at the β-position (Scheme 24).[86] When a mixture of aldehyde and dimethylzinc in THF was heated at 50 °C for 2 days, **44** was produced and isolated as β-keto lactone **45** after oxidation.



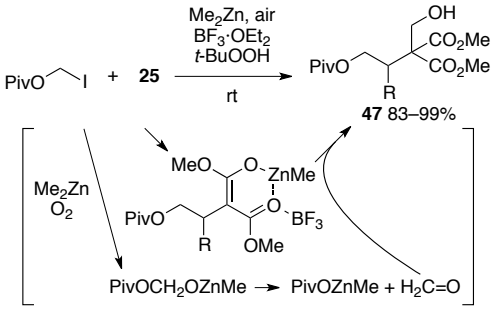
Scheme 24. Formation of **45** in the reaction of THF and aldehydes with dimethylzinc–air followed by oxidation.

The formation of this product is also explainable as a reaction of **41**. Enolate **46** would be generated from aldehyde **42**,[87] an open-ring form of **41**, and undergo an aldol reaction with the aldehyde to give **44** after hydrolysis. Our previous proposal, including intramolecular 1,4-hydrogen abstraction of THF-2-ylperoxyl radical (eq 22), was revealed to have too high activation energy based on DFT calculations.[88]



(22)

When the conjugate addition of pivaloyloxymethyl radical to alkylidenemalonates (Scheme 17) was conducted in the presence of air, α-hydroxymethylated adduct **46** was obtained (Scheme 25).[41] Formaldehyde was likely formed by oxygenation of pivaloyloxymethyl radical and reacted with the zinc enolate intermediate. In marked contrast to the zinc enolate of fumarate,[89] that of malonate did not undergo α-alkylaion either with π-allyl palladium, iodomethane, benzaldehyde, or acrylate.[77] This reaction is the only intermolecular reaction of malonate-derived zinc enolate we have ever observed.



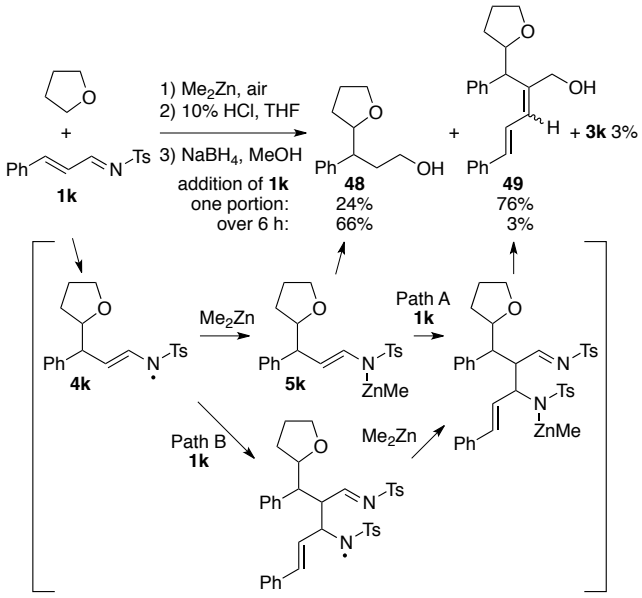
Scheme 25. α,β-Double oxymethylation of **25**.

Chain transfer step: reactions of radical intermediates

An addition reaction of the *N*-Ts enaminyl intermediate

In the reaction of *N*-Ts cinnamaldimine **1k** and THF, it was important to add **1k** slowly into the reaction mixture to obtain adduct **48** in good yield after hydrolysis and reduction (Scheme 26). When it was added in one portion, the reaction of THF with two molecules of **1k** took place, and **49** was mainly produced.

There are two possible pathways for the production of **49**. The first possibility is a Mannich-type reaction of zinc enamide intermediate **5k** and **1k**, followed by elimination of tosylamide (Path A, Scheme 26). If Path A is operative, the rate-determining step of the reaction to give **4k** should be the formation of THF-2-yl radical and not the addition step, because the slow addition of **1k** efficiently suppressed the formation of **49**. If the addition step is rate-determining,



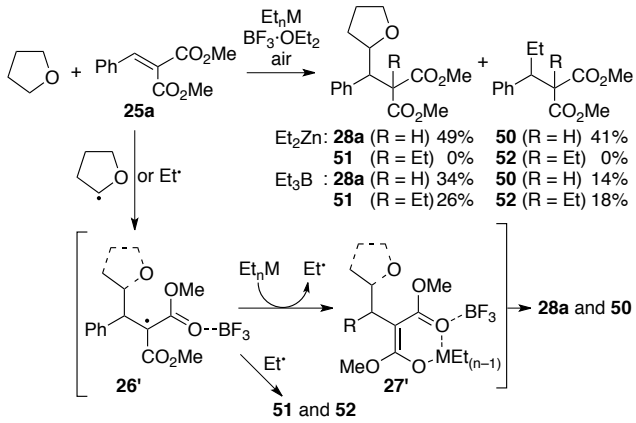
Scheme 26. Production of **49** suppressed by slow addition of **1k**.

the product ratio should be determined by the competition between THF-2-yl radical and zinc enamide **5k** to react with **1k**. Therefore, the slow addition of **1k** would reduce the rates of both reactions, and the ratio of **48** and **49** should be unchangeable. The second possibility is the addition of radical intermediate **4k** to **1k** (Path B). In Path B, the competition between dimethylzinc and **1k** to react with **4k** determines the product ratio of **48** and **49**. The slow addition kept **1k** at low concentration and would increase the possibility for **4k** to be trapped by dimethylzinc rather than to further react with **1k**. If the resulting **5k** never undergoes the further reaction to give **49**, **48** is produced after hydrolysis.

Radical coupling reactions of the intermediates

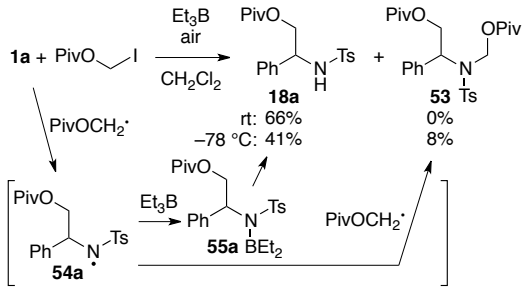
When the reaction of THF with alkylidenemalonate **25a** (Scheme 15) was conducted using triethylborane in place of dimethylzinc, significant amounts of α-ethylated products **51** and **52** were obtained (Scheme 27). In contrast, none of these byproducts were observed with diethylzinc. The α-ethylation to give **51** or **52** is probably due to the radical coupling of **26'** and ethyl radical. This indicates that the reaction of intermediate **26'** with triethylborane to give boron enolate **27'** (M = B) is so slow that the coupling reaction would compete. Accordingly, dialkylzinc should be the radical mediator of choice for the addition reaction of alkylidenemalonate.

The hetero-coupling of radical intermediates was also observed in the reactions of *N*-Ts imine. When the reaction of **1a** with iodomethyl pivalate was performed at –78 °C, *N*-alkylated product **53** was obtained as a byproduct (Scheme 28). The alkylation probably resulted from the coupling of



Scheme 27. Slow conversion of **26'** into **27'** by triethylborane resulted in the formation of **51** and **52**.

aminyl radical **54a** and pivaloyloxymethyl radical. The alternative possibility to give this product via nucleophilic substitution of the iodomethyl ester and **18a** or **55a** was excluded, because the alkylation did not occur at room temperature. Probably, the addition of pivaloyloxymethyl radical to **1a** and/or the reaction of **54a** with triethylborane were so slow at –78 °C that the radicals accumulated in such concentration for the radical coupling to compete. Similar *N*-ethylations were also reported in the addition reactions of ethyl radical to C=N bonds of *N*-Ts imine and hydrazone using triethylborane.[90]

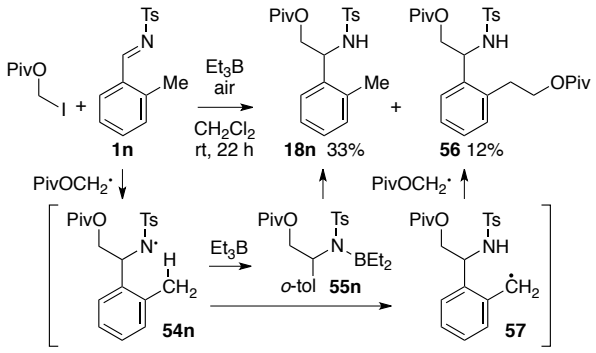


Scheme 28. *N*-Alkylation in the reaction of **1a** and iodomethyl pivalate at –78 °C.

Hydrogen transfer of the intermediates

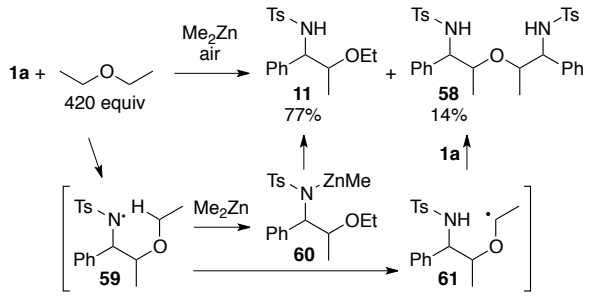
The aminyl radical intermediate undergoes not only the radical coupling but also the intramolecular hydrogen abstraction. The reaction of iodomethyl pivalate and *N*-Ts *o*-tolualdimine **1n** using triethylborane provided bispivaloyloxymethylated product **56** as well as the expected adduct **18n** (Scheme 29).[66] This product was probably produced via radical coupling between pivaloyloxymethyl radical and **57**, which resulted from intramolecular hydrogen abstraction of intermediate **54n**.

Therefore, this reaction is a cascade of three reactions: the radical addition, the intramolecular hydrogen abstraction, and the radical coupling. Importantly, neither the *N*-alkylation (Scheme 28) nor the hydrogen abstraction (Scheme 29) took place with the corresponding *N*-Boc imines,[66] showing that the reaction rates of the addition and the aminyl radical trap were both sufficiently fast.



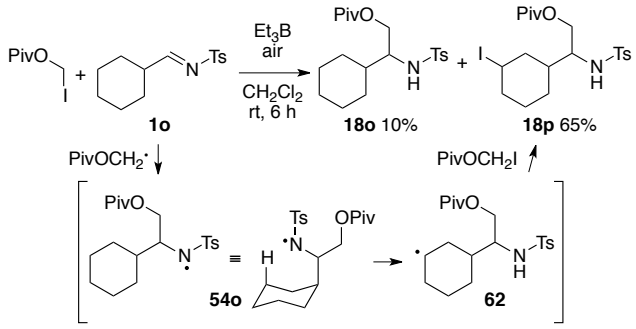
Scheme 29. Formation of **56** via intramolecular hydrogen abstraction of **54n**.

Another type of cascade reaction was observed in the reaction of *N*-Ts imine **1a** and diethyl ether using dimethylzinc. Along with the major product **11**, bisaminobenzylated product **58** was also obtained in 14% yield (Scheme 30).[91] This product was probably produced via intramolecular hydrogen transfer of aminyl radical intermediate **59** to give **61**, because intermolecular hydrogen abstraction of **11** or **60** by methyl or methoxyl radical is highly unlikely in the presence of excess amount of ether. Although the yields were quite low, these cascade reactions (Schemes 29 and 30) consist of two regioselective C–C bond forming reactions at remote positions.



Scheme 30. Formation of **59** via intramolecular hydrogen abstraction of **60**.

Recently, we succeeded in realizing a cascade reaction of the aminyl radical as the main reaction. In the reaction of cyclohexanecarbaldimine **1o** and iodomethyl pivalate using triethylborane, aminyl radical intermediate **54o** underwent intramolecular hydrogen transfer to give **62**, which abstracted iodine from iodomethyl pivalate to afford the iodinated adduct **18p** (Scheme 31).[92]



Scheme 31. Addition–hydrogen-abstraction–iodination cascade in the reaction of **1o** and iodomethyl pivalate with triethylborane.

These cascade reactions indicate that the first radical addition occurs not to the acceptors that coordinate to the radical mediators but to those without such complexation. The resulting intermediates are then trapped with the mediators or undergo the subsequent reactions. These results, however, do not deny the possibility that more Lewis basic radical acceptors would precoordinate to diethylzinc and triethylborane before undergoing addition reactions.[42c,63,64]

Summary and Outlook

In this account, our studies on radical reactions using dimethylzinc were overviewed. The use of dimethylzinc–air with C=N and C=C bonds enabled the C–C bond forming reactions accompanied with the C–H bond activation of ethers and alkanes. The generation of primary alkyl radicals was also realized without using tin reagents. These successes relied on the following characters of dimethylzinc: (1) it generates methyl radical, the least nucleophilic and least stable alkyl radical, and O-centered radical species at higher concentration than other initiators such as diethylzinc and triethylborane, and (2) it is highly reactive towards the aminyl radical and α,α-bis(alkoxycarbonyl)alkyl radical intermediates. Compared to the time when we began this study, the C–H activation with radical methodology is now a surprisingly hot field of research.[93,94] From the viewpoint of regioselectivity, however, the current technologies still have some limitations. The intramolecular hydrogen transfer process, discussed in the last section, would provide a powerful solution for this problem. Since our reports, dimethylzinc has become more and more popular as a radical initiator.[63f,89c,95,96] We believe that the advantage of dimethylzinc is still to be explored.

Acknowledgements

We greatly thank our co-workers for their contributions. We are grateful for funding from the Japan Society for the Promotion of Science and the Ministry of Education, Culture, Sports, Science and Technology, Japan. KY thanks Prof. K. U. Ingold (National Research Council), Prof. J. C. Scaiano (University of Ottawa), Prof. S. Z. Zard (Ecole Polytechnique), Prof. H. Miyabe (Hyogo University of Health Sciences), and Prof. T. Yoshimitsu (Osaka University) for helpful discussions and suggestions, and Prof. H. Matsubara (Osaka Prefecture University) for the DFT calculations.

REFERENCES

[1] M. Gomberg, *J. Am. Chem. Soc.* **1900**, *22*, 757.

[2] *Glossary of Terms Used in Physical Organic Chemistry*, IUPAC Recommendations **1994**.

[3] a) G. J. Rowlands, *Tetrahedron* **2009**, *65*, 8603 & **2010**, *66*, 1593; b) *Radicals in Synthesis I and II* (Ed.: A. Gansäuer), Topics in Current Chemistry 263 & 264, Springer-Verlag, **2006**; c) *Radicals in Organic Synthesis Vols. 1 and 2* (Eds.: P. Renaud, M. P. Sibi), Wiley-VCH, **2001**.

[4] K. U. Ingold, *Pure Appl. Chem.* **1997**, *69*, 241.

[5] C. Chatgilialoglu, *Acc. Chem. Res.* **1992**, *25*, 188.

[6] a) D. H. R. Barton, J. M. Beaton, L. E. Geller, M. M. Pechet, *J. Am. Chem. Soc.* **1960**, *82*, 2640; b) D. H. R. Barton, S. W. McCombie, *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574; c) D. H. R. Barton, D. Crich, W. B. Motherwell, *Tetrahedron* **1985**, *41*, 3901.

[7] D. P. Curran, D. M. Rakiewicz, *Tetrahedron* **1985**, *41*, 3943.

[8] a) G. Stork, P. M. Sher, H.-L. Chen, *J. Am. Chem. Soc.* **1986**, *108*, 6384; b) G. Stork, *Bull. Chem. Soc. Jpn.* **1988**, *61*, 149.

[9] a) D. J. Edmonds, D. Johnston, D. J. Procter, *Chem. Rev.* **2004**, *104*, 3371; b) H. Ishibashi, T. Sato, M. Ikeda, *Synthesis* **2002**, 695; c) M. Bertrand, L. Feray, S. Gastaldi, *C. R. Chimie* **2002**, *5*, 623; d) W. R. Bowman, C. F. Bridge, P. Brookes, *J. Chem. Soc., Perkin Trans. 1* **2000**, 1; e) L. Yet, *Tetrahedron* **1999**, *55*, 9349; f) C. Chatgilialoglu, D. Crich, M. Komatsu, I. Ryu, *Chem. Rev.* **1999**, *99*, 1991; g) T. Naito, *Heterocycles* **1999**, *50*, 505; h) B. B. Snider, *Chem. Rev.* **1996**, *96*, 339; i) C. P. Jasperse, D. P. Curran, T. L. Fevig, *Chem. Rev.* **1991**, *91*, 1237; j) B. Giese, *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds*, Pergamon Press, **1986**.

[10] *Radical Reaction Rates in Liquids* (Ed.: H. Fischer), Landolt-Börnstein Vols. II/13 & II/18, Springer-Verlag, **1984** & **1995**.

[11] a) C. Chatgilialoglu, Tin, Silicon and Related Reducing Agents. In *Radicals in Organic Synthesis Vol. 1* (Eds.: P. Renaud, M. P. Sibi), Wiley-VCH, **2001**, pp 28–49; b) W. P. Neumann, *Synthesis* **1987**, 665.

[12] Y. Kita, M. Matsugi, Radical Initiators. In *Radicals in Organic Synthesis Vol. 1* (Eds.: P. Renaud, M. P. Sibi), Wiley-VCH, **2001**, pp 1–10.

[13] V. A. Burgess, C. J. Easton, M. P. Hay, P. J. Steel, *Aust. J. Chem.* **1988**, *41*, 701.

[14] J. Byers, Atom Transfer Reactions. In *Radicals in Organic Synthesis Vol. 1* (Eds.: P. Renaud, M. P. Sibi), Wiley-VCH, **2001**, pp 72–89.

[15] a) C. Olliver, P. Renaud, *Chem. Rev.* **2001**, *101*, 3415; b) H. Yorimitsu, K. Oshima, Radical Chain Reactions: Organoborane Initiators. In *Radicals in Organic Synthesis Vol. 1* (Eds.: P. Renaud, M. P. Sibi), Wiley-VCH, **2001**, pp 11–27.

[16] a) X. Lu, S. Ma, J. Zhu, *Tetrahedron Lett.* **1988**, *29*, 5129; b) P. Girard, J. L. Namy, H. B. Kagan, *J. Am. Chem. Soc.* **1980**, *102*, 2693.

[17] a) A. Gansäuer, H. Bluhm, *Chem. Rev.* **2000**, *100*, 2771; b) G. A. Molander, *Chem. Rev.* **1992**, *92*, 29.

[18] V. Nair, J. Mathew, J. Prabhakaran, *Chem. Soc. Rev.* **1997**, *26*, 127.

[19] Reviews on ionic addition to C=N bonds: a) K. Yamada, K. Tomioka, *Chem. Rev.* **2008**, *108*, 2874; b) S. Bräse, T. Baumann, S. Dahmen, H. Vogt, *Chem. Commun.* **2007**, 1881; c) G. K. Friestad, A. K. Mathies, *Tetrahedron* **2007**, *63*, 2541; d) M. Iguchi, K. Yamada, K. Tomioka in *Organolithiums in Enantioselective Synthesis* (Ed.: D. M. Hodgson), Topics in Organometallic Chemistry, Springer, **2003**, pp 37–59. e) S. Kobayashi, H. Ishitani, *Chem. Rev.* **1999**, *99*, 1069; f) M. Arend, B. Westermann, N. Risch, *Angew. Chem. Int. Ed.* **1998**, *37*, 1044; g) S. E. Denmark, O. J.-C. Nicaise, *J. Chem. Soc., Chem. Commun.* **1996**, 999.

[20] Reviews on radical addition to C=N bonds: a) H. Miyabe, E. Yoshioka, S. Kohtani, *Curr. Org. Chem.* **2010**, *14*, 1254; b) G. K. Friestad, *Tetrahedron* **2001**, *57*, 5461; c) T. Naito, *Heterocycles* **1999**, *50*, 505; d) A. G. Fallis, I. M. Brinza, *Tetrahedron* **1997**, *53*, 17543. See also ref 9b.

[21] Addition of organolithiums to imines: a) D. Taniyama, M. Kanai, A. Iida, K. Tomioka, *Heterocycles* **1997**, *46*, 165; b) K. Tomioka, M. Satoh, D. Taniyama, M. Kanai, A. Iida, *Heterocycles* **1998**, *47*, 77; c) D. Taniyama, M. Hasegawa, K. Tomioka, *Tetrahedron: Asymmetry* **1999**, *10*, 221; d) D. Taniyama, M. Hasegawa, K. Tomioka, *Tetrahedron Lett.* **2000**, *41*, 5533; e) M. Hasegawa, D. Taniyama, K. Tomioka, *Tetrahedron* **2000**, *56*, 10153; f) K. Tomioka, Y. Shioya, Y. Nagaoka, K. Yamada, *J. Org. Chem.* **2001**, *66*, 7051.

[22] Addition of enolate to imines: a) H. Fujieda, M. Kanai, T. Kambara, A. Iida, K. Tomioka, *J. Am. Chem. Soc.* **1997**, *119*, 2060; b) T. Kambara, M. A. Hussein, H. Fujieda, A. Iida, K. Tomioka, *Tetrahedron Lett.* **1998**, *39*, 9055; c) T. Kambara, K. Tomioka, *J. Org. Chem.* **1999**, *64*, 9282; d) M. A. Hussein, A. Iida, K. Tomioka, *Tetrahedron* **1999**, *55*, 11219; e) T. Kambara, K. Tomioka, *Chem. Pharm. Bull* **1999**, *47*,

720; f) K. Tomioka, H. Fujieda, S. Hayashi, M. A. Hussein, T. Kambara, Y. Nomura, M. Kanai, K. Koga, *Chem. Commun*. **1999**, 715; g) T. Kambara, K. Tomioka, *Chem. Pharm. Bull*. **2000**, *48*, 1577; h) S. Hata, M. Iguchi, T. Iwasawa, K. Yamada, K. Tomioka, *Org. Lett.* **2004**, *6*, 1721; i) S. Hata, T. Iwasawa, M. Iguchi, K. Yamada, K. Tomioka, *Synthesis* **2004**, 1471; j) H. Fujieda, S. Hata, K. Yamada, K. Tomioka, *Heterocycles* **2005**, *66*, 603; k) S. Hata, K. Tomioka, *Tetrahedron* **2007**, *63*, 8514.

[23] Addition of dialkylzincs to imines: a) H. Fujihara, K. Nagai, K. Tomioka, *J. Am. Chem. Soc.* **2000**, *122*, 12055; b) K. Nagai, H. Fujihara, M. Kuriyama, K. Yamada, K. Tomioka, *Chem. Lett.* **2002**, 8; c) T. Soeta, K. Nagai, H. Fujihara, M. Kuriyama, K. Tomioka, *J. Org. Chem.* **2003**, *68,* 9723.

[24] Conjugate addition to alkenoate followed by Curtius rearrangement: a) Y. Asano, M. Yamashita, K. Nagai, M. Kuriyama, K. Yamada, K. Tomioka, *Tetrahedron Lett*. **2001**, *42*, 8493; b) K. Yamada, M. Yamashita, T. Sumiyoshi, K. Nishimura, K. Tomioka, *Org. Lett.* **2009**, *11*, 1631; c) Y. Yamamoto, Y. Yasuda, H. Nasu, K. Tomioka, *Org. Lett.* **2009**, *11*, 2007; d) K. Yamada, Y. Mogi, M. A. Mohamed, K. Takasu, K. Tomioka, *Org. Lett.* **2012**, *14*, 5868.

[25] Addition of lithium amide to olefins: a) H. Doi, T. Sakai, M. Iguchi, K. Yamada, K. Tomioka, *J. Am. Chem. Soc.* **2003**, *125*, 2886; b) H. Doi, T. Sakai, K, Yamada, K. Tomioka, *Chem. Commun.* **2004**, 1850; c) T. Sakai, M. Doi, Y. Kawamoto, K. Yamada, K. Tomioka, *Tetrahedron Lett.* **2004**, *45*, 9261; d) T. Sakai, Y. Kawamoto, K. Tomioka, *J. Org. Chem.* **2006**, *71*, 4706; e) T. Sakai, H. Doi, K. Tomioka, *Tetrahedron* **2006**, *62*, 8351; f) T. Ogata, A. Ujihara, S. Tsuchida, T. Shimizu, A. Kaneshige, K. Tomioka, *Tetrahedron Lett.* **2007**, *48*, 6648; g) S. Tsuchida, A. Kaneshige, T. Ogata, H. Baba, Y. Yamamoto, K. Tomioka, *Org. Lett.* **2008**, *10*, 3635; h) M. Suzuki, Y. Kawamoto, T. Sakai, Y. Yamamoto, K. Tomioka, *Org. Lett.* **2009**, *11*, 653; i) S. Harada, T. Sakai, K. Takasu, K. Yamada, Y. Yamamoto, K. Tomioka, *Chem. Asian J.* **2012**, *7*, 2196; j) S. Harada, T. Sakai, K. Takasu, K. Yamada, Y. Yamamoto, K. Tomioka, *J. Org. Chem.* **2012**, *77*, 7212; k) S. Harada, T. Sakai, K. Takasu, K. Yamada, Y. Yamamoto, K. Tomioka, *Tetrahedron* **2013**, *69*, 3264.

[26] Addition of organoboranes to imines: a) M. Kuriyama, T. Soeta, X. Hao, Q. Chen, K. Tomioka, *J. Am. Chem. Soc.* **2004**, *126*, 8128; b) X. Hao, M. Kuriyama, Q. Chen, Y. Yamamoto, K. Yamada, K. Tomioka, *Org. Lett.* **2009**, *11*, 4470; c) X. Hao, Q. Chen, M. Kuriyama, K. Yamada, Y. Yamamoto, K. Tomioka, *Catal. Sci. Tech.* **2011**, *1*, 62; d) X. Hao, Q. Chen, K. Yamada, Y. Yamamoto, K. Tomioka, *Tetrahedron* **2011**, *67*, 6469.

[27] Addition of C-nucleophiles to nitroalkenes: a) M. Yamashita, K. Yamada, K. Tomioka, *J. Am. Chem. Soc.* **2004**, *126*, 1954; b) T. Yasuhara, E. Osafune, K. Nishimura, M. Yamashita, K. Yamada, O. Muraoka, K. Tomioka, *Tetrahedron Lett*. **2004**, *45*, 3043; c) M. Yamashita, K. Yamada, K. Tomioka, *Tetrahedron* **2004**, *60*, 4237; d) T. Yasuhara, K. Nishimura, E. Osafune, O. Muraoka, K. Tomioka, *Chem. Pharm. Bull.* **2004**, *52*, 1109; e) M. Yamashita, K. Yamada, K. Tomioka, *Org. Lett.* **2005**, *7*, 2369; f) F. Valleix, K. Nagai, T. Soeta, M. Kuriyama, K. Yamada, K. Tomioka, *Tetrahedron* **2005**, *61*, 7420.

[28] K. Yamada, H. Fujihara, Y. Yamamoto, Y. Miwa, T. Taga, K. Tomioka, *Org. Lett.* **2002**, *4*, 3509.

[29] Previous reviews of our works: a) T. Akindele, K. Yamada, K. Tomioka, *Acc. Chem. Res.* **2009**, *42*, 345; b) K. Yamada, Y. Yamamoto, K. Tomioka, *J. Synth. Org. Chem. Jpn.* **2004**, *62*, 1158.

[30] a) I. Ryu, F. Araki, S. Minakata, M. Komatsu, *Tetrahedron Lett*. **1998**, *39*, 6335; b) M. P. Bertrand, L. Feray, R. Nouguier, P. Perfetti, *Synlett* **1999**, 1148; c) M. P. Bertrand, L. Feray, R. Nouguier, P. Perfetti, *J. Org. Chem*. **1999**, *64*, 9189; d) M. P. Bertrand, S. Coantic, L. Feray, R. Nouguier, P. Perfetti, *Tetrahedron* **2000**, *56*, 3951.

[31] J. Furukawa, T. Tsuruta, S. Inoue, *J. Polym. Sci.* **1957**, *26*, 234.

[32] Reviews: a) Y. A. Alexandrov, N. V. Chikinov, *J. Organomet. Chem.* **1991**, *418*, 1; b) M. Y. Zaremski, E. S. Garina, M. E. Gurskii, Y. N. Bubnov, *Polym. Sci., Ser. B* **2013**, *55*, 304.

[33] a) J. W. L. Fordham, C. L. Sturm, *J. Polym. Sci.* **1958**, *33*, 503; b) C. E. H. Bawn, D. Margerison, N. M. Richardson, *Proc. Chem. Soc.* **1959**, 397; c) N. L. Zutty, F. J. Welch, *J. Polym. Sci.* **1960**, *43*, 445; d) F. J. Welch, *J. Polym. Sci.* **1962**, *61*, 243; e) R. L. Hansen, R. R. Hamann, *J. Phys. Chem.* **1963**, *67*, 2868; f) A. L. Barney, J. M. Bruce, Jr., J. N. Coker, H. W. Jacobson, W. H. Sharkey, *J. Polym. Sci., Part A-1* **1966**, *4*, 2617; g) P. J. Krusic, J. K. Koshi, *J. Am. Chem. Soc.* **1969**, *91*, 3942; h) A. G. Davies, B. P. Roberts, *J. Organomet. Chem.* **1969**, *19*, P17; i) A. G. Davies, D. Griller, B. P. Roberts, R. Tudor, *Chem. Commun.* **1971**, 640; j) A. G. Davies, D. Griller, B. P. Roberts, *J. Chem. Soc. (B)* **1971**, 1823; k) A. G. Davies, B. P. Roberts, *J. Chem. Soc. (B)* **1971**, 1830; l) R. Rensch, H. Friboli, *Chem. Ber.* **1977**, *110*, 2189; m) P. B. Brindley, J. C. Hodgson, M. J. Scotton, *J. Chem. Soc., Perkin Trans. 2* **1979**, 45; n) R. Hunschens, R. Rensch, H. Fribolin, *Chem. Ber.* **1981**, *114*, 3581.

[34] a) M. H. Abraham, A. G. Davies, *J. Chem. Soc.* **1959**, 429; b) A. G. Davies, K. U. Ingold, P. Roberts, R. Tudor, *J. Chem. Soc. (B)* **1971**, 698.

[35] a) T. Sato, K. Hibino, T. Otsu, *Nippon Kagakukai Shi* **1975**, 1080; b) A. C. Moran, N. V. Lebedeva, S. Richert, M. D. E. Forbes, *Appl. Magn. Reson.* **2011**, *41*, 295.

[36] S. Liu, Z. Zheng, M. Li, X. Wang, *Res. Chem. Intermed.* **2012**, *38*, 1893.

[37] J. Furukawa, T. Tsuruta, T. Fueno, R. Sakata, K. Ito, *Makromol. Chem.* **1959**, *30*, 109.

[38] a) Y. Nakayama, T. Tsuruta, J. Furukawa, *Makromol. Chem.* **1960**, *40*, 79; b) A. G. Davies, B. P. Roberts, *J. Chem. Soc. (B)* **1968**, 1074.

[39] a) J. Lewiński, W. Marciniak, J. Lipkowski, I. Justyniak, *J. Am. Chem. Soc.* **2003**, *125*, 12698; b) J. Lewiński, Z. Ochal,

E, Bojarski, E. Tratkiewicz, I. Justyniak, J. Lipkowski, *Angew. Chem. Int. Ed.* **2003**, *42*, 4643; c) J. Lewiński, W. Śliwiński, M. Dranka, I. Justyniak, J. Lipkowski, *Angew. Chem. Int. Ed.* **2006**, *45*, 4826; d) D. Mukherjee, A. Ellern, A. D. Sadow, *J. Am. Chem. Soc.* **2012**, *134*, 13018.

[40] J. Maury, L. Feray, S. Bazin, J.-L. Clément, S. R. A. Marque, S. Siri, M. P. Bertrand, *Chem. Eur. J.* **2011**, *17*, 1586.

[41] K. Yamada, T. Konishi, M. Nakano, S. Fujii, R. Cadou, Y. Yamamoto, K. Tomioka, *J. Org. Chem.* **2012**, *77*, 5775.

[42] *tert*-Butyl hydroperoxide with triethylborane: a) T. Yoshimitsu, Y. Arano, H. Nagaoka, *J. Org. Chem.* **2003**, *68*, 625; c) T. Yoshimitsu, T. Makino, H. Nagaoka, *J. Org. Chem.* **2003**, *68*, 7548; d) T. Yoshimitsu, Y. Arano, H. Nagaoka, *J. Org. Chem.* **2005**, *70*, 2342.

[43] Y.-R. Luo, in *Handbook of Bond Dissociation Energies in Organic Compounds*, CRC Press, **2003**.

[44] *tert*-Butoxyl radical abstracts hydrogen from cyclohexane about 3,000 times faster than methyl radical at 300 K, $k = 7.7 \times 10^5$ and $2.5 \times 10^2\ M^{-1}s^{-1}$, respectively: a) K. Al-Niami, K. A. Holbrook, G. A. Oldershaw, *J. Chern. Soc., Faraday Trans. 2* **1989**, *85*, 1601; b) M. I. Sway, *J. Chern. Soc., Faraday Trans.* **1991**, *87*, 2157; c) Y. Guan, B. Yang, *Chem. Eng. Sci.* **2012**, *79*, 200.

[45] T. Yoshimitsu, M. Tsunoda, H. Nagaoka, *Chem. Commun.* **1999**, 1745.

[46] a) R. L. Jacobs, G. G. Ecke, G. G. *J. Org. Chem.* **1963**, *28*, 3036; b) A. J. Clark, S. Rooke, T. J. Sparey, P. C. Taylor, *Tetrahedron Lett.* **1996**, *37*, 909.

[47] K. Yamada, M. Maekawa, Y. Yamamoto, M. Nakano, T. Akindele, K. Tomioka, *Tetrahedron Lett.* **2009**, *50*, 6040.

[48] W. K. Busfield, D. Grice, I. D. Jenkins, *J. Chem. Soc., Perkin Trans. 2* **1994**, 1079.

[49] M. Kubisiak, K. Zelga, W. Bury, I. Justyniak, K. Budny-Godlewski, Z. Ochal, J. Lewiński, *Chem. Sci.* **2015**, *6*, 3102.

[50] H. Matsubara, S. Suzuki, S. Hirano, *Org. Biomol. Chem.* **2015**, *13,* 4686.

[51] V. Malatesta, J. C. Scaiano, *J. Org. Chem.* **1982**, *47*, 1455.

[52] G. Brunton, K. U. Ingold, B. P. Roberts, A. L. J. Beckwith, P. J. Krusic, *J. Am. Chem. Soc.* **1977**, *99*, 3177.

[53] K. Yamada, Y. Yamamoto, M. Maekawa, K. Tomioka, *J. Org. Chem.* **2004**, *69*, 1531.

[54] T. Akindele, Y. Yamamoto, M. Maekawa, H. Umeki, K. Yamada, K. Tomioka, *Org. Lett.* **2006**, *8*, 5729.

[55] K. Yamada, Y. Yamamoto, M. Maekawa, J. Chen, K. Tomioka, *Tetrahedron Lett.* **2004**, *45*, 6595.

[56] K. Yamada, Y. Yamamoto, M. Maekawa, T. Akindele, H. Umeki, K. Tomioka, *Org. Lett.* **2006**, *8*, 87.

[57] The tin method sometimes fails: G. K. Friestad, C. Draghici, M. Soukri, J. Qin, *J. Org. Chem.* **2005**, *70*, 6330.

[58] L. Micouin, P. Knochel, *Synlett* **1997**, 327.

[59] P. Knochel, *Synlett* **1995**, 393.

[60] K. Yamada, M. Nakano, M. Maekawa, T. Akindele, K. Tomioka, *Org. Lett.* **2008**, *10*, 3805.

[61] $k = 3.4 \times 10^5\ M^{-1}s^{-1}$ at 50 °C: M. Newcomb, R. M. Sanchez, J. Kaplan, *J. Am. Chem. Soc.* **1987**, *109*, 1195.

[62] K. Yamada, Y. Yamamoto, K. Tomioka, *Org. Lett.* **2003**, *5*, 1797.

[63] a) M. P. Bertrand, L. Feray, R. Nouguier, L. Stella, *Synlett* **1998**, 780; b) M. P. Bertrand, L. Feray, R. Nouguier, P. Perfetti, *Synlett* **1999**, 1148; c) M. P. Bertrand, L. Feray, R. Nouguier, P. Perfetti, *J. Org. Chem.* **1999**, *64*, 9189; d) M. P. Bertrand, S. Coantic, L. Feray, R. Nouguier, P. Perfetti, *Tetrahedron* **2000**, *56*, 3951; e) S. Bazin, L. Feray, N. Vanthuyne, M. P. Bertrand, *Tetrahedron* **2005**, *61*, 4261; f) S. Bazin, L. Feray, N. Vanthuyne, D. Siri, M. P. Bertrand, *Tetrahedron* **2007**, *63*, 77.

[64] a) H. Miyabe, M. Ueda, N. Yoshioka, T. Naito, *Synlett* **1999**, 465; b) H. Miyabe, C. Ushiro, M. Ueda, K. Yamakawa, T. Naito, *J Org. Chem.* **2000**, *65*, 176; c) H. Miyabe, M. Ueda, N. Yoshioka, K. Yamakawa, T. Naito, *Tetrahedron* **2000**, *56*, 2413; d) H. Miyabe, M. Ueda, T. Naito, *Synlett* **2004**, 1140; e) H. Miyabe, R. Asada, Y. Takemoto, *Tetrahedron* **2005**, *61*, 385; f) M. Nakakoshi, M. Ueda, S. Sakurai, K. Asakura, H. Utsumi, O. Miyata, T. Naito, Y. Takahashi, *Magn. Reson. Chem.* **2007**, *45*, 989.

[65] In the following literature, ^{11}B NMR signals at –53 ppm were assigned as signals of borane–carbonyl complexes, [Et_3B^-–O^+=C<], without any citation. Since the chemical shifts were the same as those of oxygenated borane, such as Et_2BOEt, the report should be interpreted carefully: V. Beraud, Y. Gnanou, J. C. Walton, B. Maillard, *Tetrahedron Lett.* **2000**, *41*, 1195. See also refs. 71 and 72.

[66] K. Yamada, T. Konishi, M. Nakano, S. Fujii, R. Cadou, Y. Yamamoto, K. Tomioka, *J. Org. Chem.* **2012**, *77*, 1547.

[67] F. G. Bordwell, H. E. Fried, D. L. Hughes, T. Y. Lynch, A. V. Satish, Y. E. Whang, *J. Org. Chem.* **1990**, *55*, 3330.

[68] F. G. Bordwell, H. E. Fried, *J. Org. Chem.* **1991**, *56*, 4218.

[69] F. G. Bordwell, D. J. Algrim, *J. Am. Chem. Soc.* **1988**, *110*, 2964.

[70] S. Fujii, K. Yamada, unpublished work.

[71] The chemical shifts of neat Et_3B (–86.5) and a THF solution (–80.3) differ only by 6.2 ppm, suggesting difficulty in detecting the interaction of Et_3B and carbonyl oxygen by NMR: L. H. Toporcer, R. E. Dessy, S. I. E. Green, *Inorg. Chem.* **1965**, *4*, 1649.

[72] The chemical shift of the expected borate complex is presumably around 0 ppm based on reported chemical shifts, e.g., Et_3B-NMe_3 –4.3 ppm: H. Noth, H. Vahrenkamp, *Chem. Ber.* **1966**, *99*, 1049.

[73] Fujii, S.; Konishi, T.; Matsumoto, Y.; Yamaoka, Y.; Takasu, K.; Yamada, K. *J. Org. Chem.* **2014**, *79*, 8128.

[74] Recent examples: a) J. A. Fernández-Salas, M. M. Rodríguez-Fernández, M. C. Maestro, J. L. García-Ruano, *Chem. Commun.* **2014**, *50*, 6046; b) J. A. Fernández-Salas, M. M. Rodríguez-Fernández, M. C. Maestro, J. L. García-Ruano, *Eur. J. Org. Chem.* **2014**, 5265; c) E. M. Rochette, W. Lewis, A. G. Dossetter, R. A. Stockman, *Chem. Commun.* **2013**, *49*, 9395; d) J, A. Fernández-Salas, M. C. Maestro, M. M. Rodríguez-Fernández, J. L. García-Ruano, I. Alonso, *Org. Lett.* **2013**, *15*, 1658.

[75] T. Akindele, K. Yamada, T. Sejima, M. Maekawa, Y. Yamamoto, M. Nakano, K. Tomioka, *Chem. Pharm. Bull.* **2010**, *58*, 265.

[76] K. Yamada, H. Umeki, M. Maekawa, Y. Yamamoto, T. Akindele, M. Nakano, K. Tomioka, *Tetrahedron* **2008**, *64*, 7258.

[77] M. Maekawa, Chemoselective Radical Conjugate Addition of Ethers Using Dimethylzinc. Ph.D. Thesis, Kyoto University, March 2008.

[78] K. Yamada, M. Maekawa, T. Akindele, M. Nakano, Y. Yamamoto, K. Tomioka, *J. Org. Chem.* **2008**, *73*, 9535.

[79] J. R. Zimmerman, M. Manpadi, R. Spatney, A. Baker, *J. Org. Chem.* **2011**, *76*, 8076.

[80] Cyclization of 4-formylbutyl, $k = 8.7 \times 10^5\ s^{-1}$; ring-opening of cyclopentyloxyl, $k = 8.7 \times 10^8\ s^{-1}$ at 80 °C: A. L. J. Beckwith, B. P. Hay, *J. Am. Chem. Soc.* **1989**, *111*, 2674.

[81] Y. Yamamoto, K. Yamada, K. Tomioka, unpublished work.

[82] a) D. L. J. Clive, M. H. D. Postema, *Chem. Commun.* **1993**, 429; b) P. Devin, L. Fensterbank, M. Malacria, *Tetrahedron Lett.* **1998**, *39*, 833; c) P. Devin, L. Fensterbank, M. Malacria, *Tetrahedron Lett.* **1999**, *40*, 5511; d) M. Chareyron, P. Devin, L. Fensterbank, M. Malacria, *Synlett* **2000**, 83.

[83] K. Yamada, M. Maekawa, T. Akindele, Y. Yamamoto, M. Nakano, K. Tomioka, *Tetrahedron* **2009**, *65*, 903.

[84] B. Maillard, K. U. Ingold, J. C. Scaiano, *J. Am. Chem. Soc.* **1983**, *105*, 5095.

[85] Y. Yamamoto, M. Maekawa, T. Akindele, K. Yamada, K. Tomioka, *Tetrahedron* **2005**, *61*, 379.

[86] Y. Yamamoto, K. Yamada, K. Tomioka, *Tetrahedron Lett.* **2004**, *45*, 795.

[87] Dialkylzinc was utilized as a base to generate zinc enolate species: a) Y. Kawakami, T. Tsuruta, *Bull. Chem. Soc. Jpn.* **1971**, *44*, 247; b) M. M. Hansen, P. A. Bartlett, C. H. Heathcock, *Organometallics* **1987**, *6*, 2069; c) X. Xu, B. Liu, Y. Zou, Y. Guo, L. Li, Y. Liu, *Adv. Funct. Mater.* **2012**, *22*, 4139; d) O. S. Shneider, E. Pisarevsky, P. Fristrup, A. M. Szpilman, *Org. Lett.* **2015**, *17*, 282. See also ref 41.

[88] The activation energy was 171 kJ/mol at BHandHLYP/cc-pVDZ level of calculations: H. Matsubara, S. Suzuki, Osaka Prefecture University, unpublished work.

[89] a) S. Bazin, L. Feray, N. Vanthuyne, M. P. Bertrand, *Tetrahedron* **2005**, *61*, 4261; b) S. Bazin, L. Feray, N. Vanthuyne, D. Siric, M. P. Bertrand, *Tetrahedron* **2007**, *63*, 77; c) J. Maury, L. Feray, P. Perfetti, M. P. Bertrand, *Org. Lett.* **2010**, *12*, 3590.

[90] a) H. Miyabe, M. Ueda, T. Naito, *Chem. Commun.* **2000**, 2059; b) H. Miyabe, M. Ueda, A. Nishimura, T. Naito, *Tetrahedron* **2004**, *60*, 4227; c) M. Ueda, H. Miyabe, O. Miyata, T. Naito, *Tetrahedron* **2009**, *65*, 1321.

[91] K. Yamada, K. Tomioka, unpublished work.

[92] S. Fujii, M. Nakano, Y. Yamaoka, K. Takasu, K. Yamada, K. Tomioka, *Tetrahedron Lett.*, in press. DOI: 10.1016/j.tetlet.2014.11.105.

[93] Reviews: a) S.-Y. Zhang, F.-M. Zhang, Y.-Q. Tu, *Chem. Soc. Rev.* **2011**, *40*, 1937; b) B. Rossi, S. Prosperini, N. Pastori, A. Clerici, C. Punta, *Molecules* **2012**, *17*, 14700.

[94] Recent examples: a) S. Kamijo, M. Hirota, K. Tao, M. Watanabe, T. Murafuji, *Tetrahedron Lett.* **2014**, *55*, 5551; b) Y. Amaoka, M. Nagatomo, M. Watanabe, K. Tao, S. Kamijo, M. Inoue, *Chem. Sci.* **2014**, *5*, 4339; c) J. Zhang, P. Li, L. Wang, *Org. Biomol. Chem.* **2014**, *12*, 2969; d) E. B. Averina, D. A. Vasilenko, Y. V. Samoilichenko, Y. K. Grishin, V. B. Rybakov, T. S. Kuznetsova, N. S. Zefirov, *Synthesis* **2014**, *46*, 1107; e) G. Bergonzini, C. S. Schindler, C.-J. Wallentin, E. N. Jacobsen, C. R. J. Stephenson, *Chem. Sci.* **2014**, *5*, 112; f) X. Hao, C. Liu, C. Liu, Y. Chen, X. Zhao, M. Song, R. Qian, H. Guo, *Tetrahedron Lett.* **2013**, *54*, 6964; g) L. Zhang, Y. Deng, F. Shi, *Tetrahedron Lett.* **2013**, *54*, 5217; h) Y. Amaoka, M. Nagatomo, M. Inoue, *Org. Lett.* **2013**, *15*, 2160; i) T. Hoshikawa, S. Kamijo, M. Inoue, *Synthesis* **2013**, *45*, 874; j) T. Hoshikawa, S. Kamijo, M. Inoue, *Org. Biomol. Chem.* **2013**, *11*, 164; k) B. Rossi, N. Pastori, A. Clerici, C. Punta, *Tetrahedron* **2012**, *68*, 10151; l) T. Sonobe, K. Oisaki, M. Kanai, *Chem. Sci.* **2012**, *3*, 3249; m) S. R. Wang, Z. Qiu, Z. Xie, *J. Am. Chem. Soc.* **2011**, *133*, 5760; n) S. Kamijo, T. Hoshikawa, M. Inoue, *Org. Lett.* **2011**, *13*, 5928; o) S. Hashizume, K. Oisaki, M. Kanai, *Org. Lett.* **2011**, *13*, 4288; p) S. Kamijo, T. Hoshikawa, M. Inoue, *Tetrahedron Lett.* **2011**, *52*, 2885; q) T. Kamon, Y. Irifune, T. Tanaka, T. Yoshimitsu, *Org. Lett.* **2011**, *13*, 2674; r) D. Ravelli, A. Albini, M. Fagnoni, *Chem. Eur. J.* **2011**, *17*, 572; s) L. Troisi, C. Granito, L. Ronzini, F. Rosato, V. Videtta, *Tetrahedron Lett.* **2010**, *51*, 5980; t) M. D. Tzirakis, M. Orfanopoulos, *Angew. Chem. Int. Ed.* **2010**, *49*, 5891; u) J. Y. Lee, K.-C. Lim, X. Meng, S. Kim, *Synlett* **2010**, 1647; v) Z. Li, R. Yu, H. Li, *Angew. Chem. Int. Ed.* **2008**, *47*, 7497; w) G. Deng, C.-J. Li , *Tetrahedron Lett.* **2008**, *49*, 5601; x) A. Sato, H. Yorimitsu, K. Oshima, *Chem. Asian J.* **2007**, *2*, 1568; y) G. K. Friestad, C. Draghici, M. Soukri, J. Qin, *J. Org. Chem.* **2005**, *70*, 6330.

[95] Reviews: a) F. Chemla, F. Dulong, F. Ferreira, M. P. Nüllen, A. Pérez-Luna, *Synthesis* **2011**, 1347; b) S. Bazin, L. Feray, M. P. Bertrand, *Chimia* **2006**, *60*, 260.

[96] Recent examples: a) F. Chemla, F. Dulong, F. Ferreira, A. Pérez-Luna, *Beilstein J. Org. Chem.* **2013**, *9*, 236; b) J. Maury, D. Mouysset, L. Feray, S. R. A. Marque, D. Siri, M. P. Bertrand, *Chem. Eur. J.* **2012**, *18*, 3241; c) J. Maury, L. Feray, M. P. Bertrand, *Org. Lett.* **2011**, *13*, 1884; d) Z. Chen,

Y.-X. Zhang, Y. An, X.-L. Song, Y.-H. Wang, L.-L. Zhu, L. Guo, *Eur. J. Org. Chem.* **2009**, 5146; e) E. Mileo, F. Benfatti, P. G. Cozzi, M. Lucarini, *Chem Commun.* **2009**, 469; f) M. Á. Fernández-Ibáñez, B. Maciá, A. J. Minnaard, B. L. Feringa, *Org. Lett.* **2008**, *10*, 4041; g) L. Feray, M. P. Bertrand, *Eur. J. Org. Chem.* **2008**, 3164; h) M. Á. Ferná ndez-Ibáñez, B. Maciá, A. J. Minnaard, B. L. Feringa, *Angew. Chem. Int. Ed.* **2008**, *47*, 1317; i) F. Cougnon, L. Feray, S. Bazin, M. P. Bertrand, *Tetrahedron* **2007**, *63*, 11959; j) P. G. Cozzi, *Adv. Synth. Catal.* **2006**, *348*, 2075; k) M. J. Alves, G. Fortes, E. Guimarães, A. Lemos, *Synlett* **2003**, 1403.